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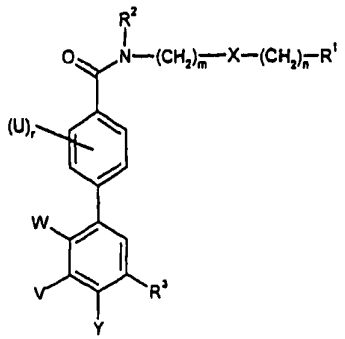
(54) Title: 5'-CARBAMOYL-1,1'-BIPHENYL-4-CARBOXAMIDE DERIVATIVES AND THEIR USE AS P38 KINASE INHIBITORS



(I)

(57) Abstract: Compounds of formula (I): wherein X is a bond or a phenyl group which may be optionally substituted; R^1 is selected from an optionally substituted five- to seven-membered heterocyclic ring, an optionally substituted five- to seven-membered heteroaryl ring and an optionally substituted fused bicyclic ring; R^2 is selected from hydrogen, C_{1-6} alkyl and $-(CH_2)_p-C_{3-7}$cycloalkyl; or when X is a bond and m and n are both zero R^1 and R^2, together with the nitrogen atom to which they are bound, form a five- to six-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen and nitrogen, which can be optionally substituted by C_{1-4}alkyl; R^3 is the group $-CO-NH-(CH_2)_q-R^4$; U is selected from methyl and halogen; W is selected from methyl and chlorine; V and Y are each selected independently from hydrogen, methyl and halogen; Z is selected from -O- and a bond; m and n are independently selected from 0, 1 and 2, wherein each carbon atom of the resulting carbon chain may be optionally substituted with up to two groups selected independently from C_{1-4}alkyl, and the sum of m+ n is from 0 to 4; p is selected from 0 and 1; q and s are selected from 0, 1 and 2; r is selected from 0, 1 and 2; or pharmaceutically acceptable salts or solvated thereof, and their use as pharmaceuticals, particularly as p38 kinase inhibitors.

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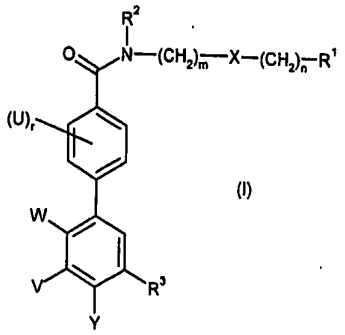
5'-CARBAMOYL-1,1'-BIPHENYL-4-CARBOXAMIDE DERIVATIVES AND THEIR USE AS P38 KINASE INHIBITORS

This invention relates to novel compounds and their use as pharmaceuticals, particularly as p38 kinase inhibitors, for the treatment of certain diseases and conditions.

We have now found a group of novel compounds that are inhibitors of p38 kinase.

According to the invention there is provided a compound of formula (I):



(I)

wherein

X is a bond or a phenyl group which may be optionally substituted;

R^1 is selected from an optionally substituted five- to seven-membered heterocyclic ring, an optionally substituted five- to seven-membered heteroaryl ring and an optionally substituted fused bicyclic ring;

R^2 is selected from hydrogen, C_{1-6}alkyl and $-(CH_2)_p-C_{3-7}$cycloalkyl;

or when X is a bond and m and n are both zero, R^1 and R^2, together with the nitrogen atom to which they are bound, form a five- to six-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen and nitrogen, which can be optionally substituted by C_{1-4}alkyl;

R^3 is the group $-CO-NH-(CH_2)_q-R^4$;

when q is 0 to 2 R^4 is selected from hydrogen, C_{1-6}alkyl, $-C_{3-7}$cycloalkyl, $CONHR^5$, phenyl optionally substituted by R^7 and/or R^8, heteroaryl optionally substituted by R^7 and/or R^8 and heterocyclyl optionally substituted by R^7 and/or R^8;

and when q is 2 R^4 is additionally selected from C_{1-6}alkoxy, $NHCOR^5$, $NHCONHR^6$, NR^5R^6, and OH;

R^5 is selected from hydrogen, C_{1-6}alkyl and phenyl wherein the phenyl group may be optionally substituted by up to two substituents selected from C_{1-6}alkyl and halogen;

R^6 is selected from hydrogen and C_{1-6}alkyl;

or R^5 and R^6, together with the nitrogen atom to which they are bound, form a five- to six-membered heterocyclic or heteroaryl ring optionally containing one additional heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring may be substituted by up to two C_{1-6}alkyl groups;

R^7 is selected from C_{1-6}alkyl, C_{1-6}alkoxy, $-CONR^6R^9$, $-NHCOR^9$, $-SO_2NHR^9$, $-NHSO_2R^9$, halogen, trifluoromethyl, $-Z-(CH_2)_s$-phenyl optionally substituted by one or more halogen atom, $-Z-(CH_2)_s$-heterocyclyl or $-Z-(CH_2)_s$-heteroaryl wherein the heterocyclyl or heteroaryl group may be optionally substituted by one or more substituents selected from C_{1-6}alkyl;

R^8 is selected from C_{1-6}alkyl and halogen;

or when R^7 and R^8 are ortho substituents, then together with the carbon atoms to which they are bound, R^7 and R^8 may form a five- or six-membered saturated or unsaturated ring to give a fused bicyclic ring system, wherein the ring that is formed by R^7 and R^8 may optionally contain one or two heteroatoms selected from oxygen, nitrogen and sulfur;

R^9 is selected from hydrogen and C_{1-6}alkyl;

U is selected from methyl and halogen;

W is selected from methyl and chlorine;

V and Y are each selected independently from hydrogen, methyl and halogen;

Z is selected from -O- and a bond;

m and n are independently selected from 0, 1 and 2, wherein each carbon atom of the resulting carbon chain may be optionally substituted with up to two groups selected independently from C_{1-6}alkyl, and the sum of m+ n is from 0 to 4;

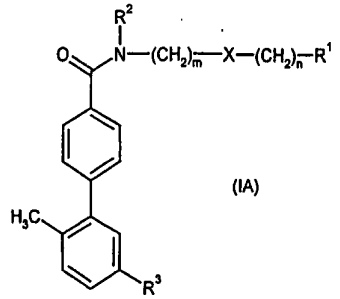
p is selected from 0 and 1;

q and s are selected from 0, 1 and 2;

r is selected from 0, 1 and 2;

or a pharmaceutically acceptable salt or solvate thereof.

According to a further embodiment of the invention there is provided a compound of formula (IA):



(IA)

wherein R^1, R^2, R^3, m, n and X are as defined above, or a pharmaceutically acceptable salt or solvate thereof.

In a preferred embodiment, the molecular weight of a compound of formula (I) does not exceed 1000, more preferably 800, even more preferably 600.

The group R^1 may be optionally substituted by up to three substituents, more preferably one or two substituents, selected from C_{1-6}alkyl, C_{1-6}alkoxy, oxy, halogen, hydroxyC_{1-6}alkyl, -N(C_{1-6}alkyl)$_2$, -CH_2-N(C_{1-6}alkyl)$_2$, -CO_2C_{1-6}alkyl, phenyl optionally substituted by halogen and benzyl optionally substituted by halogen and/or cyano.

When X is phenyl, the optional substituents for X are selected independently from C_{1-6}alkyl, C_{1-6}alkoxy, halogen, trifluoromethyl, trifluoromethoxy, and cyano. Particularly preferred substituents are methyl, chloro, fluoro, cyano, methoxy and trifluoromethoxy. X may also be optionally substituted by C_{3-7}cycloalkyl.

In a preferred embodiment, when X is phenyl, R^1 is preferably an optionally substituted group selected from pyrrolidinyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, tetrazolyl, oxazolyl, oxadiazolyl, piperidinyl, piperazinyl, morpholino, pyridyl, pyrimidinyl, thienyl, imidazolidinyl, benzimidazolyl and quinolyl. Particularly preferred groups are morpholino, pyrrolidinyl, imidazolyl, pyridyl, oxazolyl, oxadiazolyl, pyrazolyl, piperidinyl, piperazinyl and pyrimidinyl. The optional substituents for R^1 when X is phenyl are selected independently from C_{1-6}alkyl, C_{1-6}alkoxy, oxy, halogen, hydroxyC_{1-6}alkyl, -N(C_{1-6}alkyl)$_2$ and -CH_2-N(C_{1-6}alkyl)$_2$. Particularly preferred optional substituents are methyl and oxy.

In a preferred embodiment, when X is a bond, R^1 is selected from an optionally substituted pyrrolidinyl, isoxazolyl, furyl, thienyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, thiazolyl, oxadiazolyl, piperidinyl, piperazinyl, morpholino, pyridyl, tetrahydrofuranyl, tetrahydrothiophenyl and quinolyl. Particularly preferred groups are piperazinyl, piperidinyl, morpholino, imidazolyl, thienyl and pyrrolidinyl. The optional substituents for R^1 when X is a bond are selected independently from C_{1-6}alkyl, C_{1-6}alkoxy, oxy, halogen, hydroxyC_{1-6}alkyl, -N(C_{1-6}alkyl)$_2$, -CH_2-N(C_{1-6}alkyl)$_2$, -CO_2C_{1-6}alkyl, phenyl optionally substituted by halogen and benzyl optionally substituted by halogen and/or cyano. Particularly preferred optional substituents are methyl and oxy.

In a preferred embodiment, R^2 is selected from hydrogen, C_{1-4}alkyl and –CH_2-cyclopropyl, more preferably hydrogen.

In a preferred embodiment, R^4 is selected from C_{1-4}alkyl, cyclopropyl, -CH_2-cyclopropyl, pyridinyl and phenyl.

In a preferred embodiment, R^5 is selected from hydrogen and C_{1-4}alkyl, and phenyl optionally substituted by methyl or halogen.

In a preferred embodiment, R^6 is selected from hydrogen and C_{1-4}alkyl.

In a preferred embodiment, R^7 is selected from C_{1-4}alkyl, -NHCOCH$_3$, pyridinyl, pyrimidinyl and oxadiazolyl.

In a preferred embodiment, R^8 is hydrogen.

In a preferred embodiment, R^9 is C_{1-4}alkyl.

In a preferred embodiment, W is methyl.

In a preferred embodiment, V and Y are each selected independently from hydrogen, chlorine and fluorine. In a further preferred embodiment, V is fluorine.

In a preferred embodiment, Z is a bond

In a preferred embodiment, m and n are independently selected from 0, 1 and 2, and the sum of m+n is from 0-3.

In a preferred embodiment, q is selected from 0 and 1.

In a preferred embodiment, s is selected from 0 and 1.

In a preferred embodiment, r is selected from 0 and 1. In particular, r is 0.

It is to be understood that the present invention covers all combinations of particular and preferred groups described hereinabove.

Particular compounds according to the invention include those mentioned in the examples and their pharmaceutically acceptable salts and solvates. A specific example which may be mentioned is:

N^3-Cyclopropyl-$N^{4'}$-(3-imidazol-1-ylpropyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide.

Further specific examples which may be mentioned include:

N^3-Cyclopropyl-6-methyl-$N^{4'}$-[4-(4-methylpiperazin-1-yl)benzyl]-1,1'-biphenyl-3,4'-dicarboxamide;

N^3-Cyclopropyl-6-methyl-$N^{4'}$-(1,3-thiazol-2-ylmethyl)-1,1'-biphenyl-3,4'-dicarboxamide;

N^3-Cyclopropyl-5-fluoro-6-methyl-$N^{4'}$-[3-(morpholin-4-ylmethyl)benzyl]-1,1'-biphenyl-3,4'-dicarboxamide;

N^3-Cyclopropyl-6-methyl-$N^{4'}$-[3-(morpholin-4-ylmethyl)benzyl]-1,1'-biphenyl-3,4'-dicarboxamide;

N^3-Cyclopropyl-6-methyl-$N^{4'}$-{2-[(4-methylpiperazin-1-yl)methyl]phenyl}-1,1'-biphenyl-3,4'-dicarboxamide;

tert-Butyl 4-{[({5'-[(cyclopropylamino)carbonyl]-2'-methyl-1,1'-biphenyl-4-yl}carbonyl)amino]methyl}piperidine-1-carboxylate;

N^3-Cyclopropyl-6-methyl-$N^{4'}$-[3-(pyrrolidin-1-ylmethyl)benzyl]-1,1'-biphenyl-3,4'-dicarboxamide;

N^3-Cyclopropyl-6-methyl-$N^{4'}$-{3-[(4-methylpiperazin-1-yl)methyl]benzyl}-1,1'-biphenyl-3,4'-dicarboxamide; and

N^3-Cyclopropyl-6-methyl-$N^{4'}$-[3-(piperidin-1-ylmethyl)benzyl]-1,1'-biphenyl-3,4'-dicarboxamide.

As used herein, the term "alkyl" refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms. For example, C_{1-6}alkyl means a straight or branched alkyl containing at least 1, and at most 6, carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, isobutyl, isopropyl and t-butyl. A C_{1-4}alkyl group is preferred, for example methyl, ethyl or isopropyl. The said alkyl groups may be optionally substituted with one or more halogen atoms, in particular fluorine atoms, for example, trifluoromethyl.

As used herein, the term "alkoxy" refers to a straight or branched chain alkoxy group, for example, methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy, 2-methylprop-1-oxy, 2-methylprop-2-oxy, pentoxy, or hexyloxy. A C_{1-4}alkoxy group is preferred, for example methoxy or ethoxy.

As used herein, the term "cycloalkyl" refers to a non-aromatic hydrocarbon ring containing the specified number of carbon atoms. For example, C_{3-7}cycloalkyl means a non-aromatic ring containing at least three, and at most seven, ring carbon atoms. Examples of "cycloalkyl" as used herein include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. A C_{3-6} cycloalkyl group is preferred, for example cyclopropyl.

As used herein, the terms "heteroaryl ring" and "heteroaryl" refer to an monocyclic five- to seven-membered unsaturated hydrocarbon ring containing at least one heteroatom independently selected from oxygen, nitrogen and sulfur. Preferably, the heteroaryl ring has five or six ring atoms. Examples of heteroaryl rings include, but are not limited to, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl. The said ring may be optionally substituted by one or more substituents independently selected from C_{1-6}alkyl and oxy.

As used herein, the terms "heterocyclic ring" or "heterocyclyl" refer to a monocyclic three- to seven-membered saturated or non-aromatic, unsaturated hydrocarbon ring containing at least one heteroatom independently selected from oxygen, nitrogen and sulfur. Preferably, the heterocyclyl ring has five or six ring atoms. Examples of heterocyclyl groups include, but are not limited to, aziridinyl, pyrrolinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, piperidyl, piperazinyl, morpholino, tetrahydropyranyl, tetrahydrofuranyl, and thiomorpholino. The said ring may be optionally substituted by one or more substituents independently selected from C_{1-6}alkyl and oxy.

As used herein, the term "fused bicyclic ring" refers to a ring system comprising two five- to seven-membered saturated or unsaturated rings, the ring system containing at least one heteroatom independently selected from oxygen, nitrogen and sulfur. Preferably, each ring has five or six ring atoms. Examples of suitable fused bicyclic

rings include, but are not limited to, naphthyl, indolyl, indolinyl, benzothienyl, quinolyl, isoquinolyl, tetrahydroquinolyl, benzodioxanyl, indanyl and tetrahydronaphthyl. Each ring may be optionally substituted with one or more substituents selected from halogen, C_{1-6}alkyl, oxy, $-(CH_2)_pNR^{10}R^{11}$, $-CO(CH_2)_pNR^{10}R^{11}$, and imidazolyl. Particularly preferred substituents are chlorine, imidazolyl and $-CH_2-N(CH_3)_2$.

As used herein, the terms "halogen" or "halo" refer to the elements fluorine, chlorine, bromine and iodine. Preferred halogens are fluorine, chlorine and bromine. A particularly preferred halogen is fluorine.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s) which occur and events that do not occur.

As used herein, the term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I) or a salt thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include water, ethanol and acetic acid. Most preferably the solvent used is water.

Certain compounds of formula (I) may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms or may exhibit cis-trans isomerism). The individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the present invention. The present invention also covers the individual isomers of the compounds represented by formula (I) as mixtures with isomers thereof in which one or more chiral centres are inverted. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

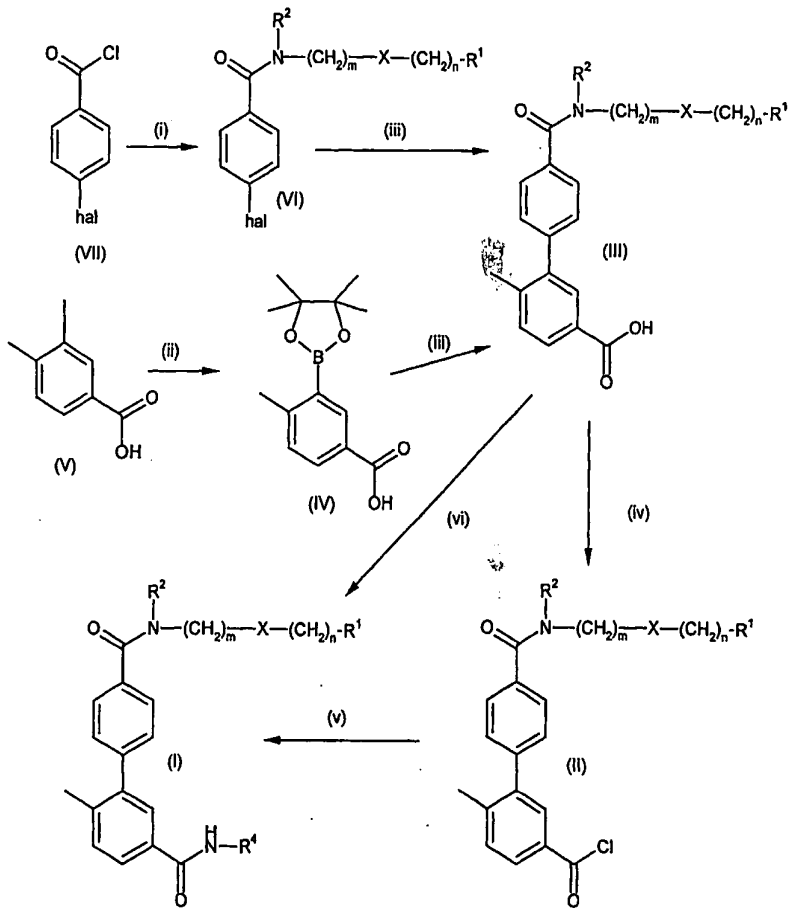
Salts of the compounds of the present invention are also encompassed within the scope of the invention and may, for example, comprise acid addition salts resulting from reaction of an acid with a nitrogen atom present in a compound of formula (I).

Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. Representative salts include the following salts: Acetate, Benzenesulfonate, Benzoate, Bicarbonate, Bisulfate, Bitartrate, Borate, Bromide, Calcium Edetate, Camsylate, Carbonate, Chloride, Clavulanate, Citrate, Dihydrochloride, Edetate, Edisylate, Estolate, Esylate, Fumarate, Gluceptate, Gluconate, Glutamate, Glycollylarsanilate, Hexylresorcinate, Hydrabamine, Hydrobromide, Hydrochloride, Hydroxynaphthoate, Iodide, Isethionate, Lactate,

Lactobionate, Laurate, Malate, Maleate, Mandelate, Mesylate, Methylbromide, Methylnitrate, Methylsulfate, Monopotassium Maleate, Mucate, Napsylate, Nitrate, N-methylglucamine, Oxalate, Pamoate (Embonate), Palmitate, Pantothenate, Phosphate/diphosphate, Polygalacturonate, Potassium, Salicylate, Sodium, Stearate, Subacetate, Succinate, Tannate, Tartrate, Teoclate, Tosylate, Triethiodide, Trimethylammonium and Valerate. Other salts which are not pharmaceutically acceptable may be useful in the preparation of compounds of this invention and these form a further aspect of the invention.

The compounds of this invention may be made by a variety of methods, including standard chemistry. Any previously defined variable will continue to have the previously defined meaning unless otherwise indicated. Illustrative general synthetic methods are set out below and then specific compounds of the invention are prepared in the working Examples.

For example, a general method (A) for preparing the compounds of Formula (I) comprises the reactions set out in Scheme 1 below.

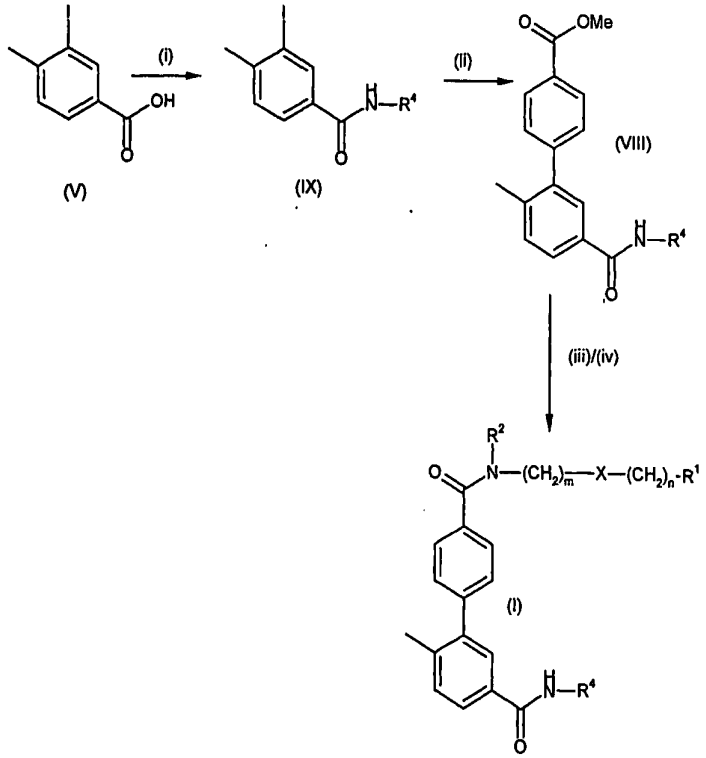


Scheme 1

(i) $R^1(CH_2)_nX(CH_2)_mN\ R^2H$, Et_3N, THF
(ii) Bis(pinnacolato)diboron, $PdCl_2dppf$, KOAc, DMF
(iii) $(Ph_3P)_4Pd$, Na_2CO_3, DME
(iv) $(COCl)_2$, DMF
(v) R^4NH_2, pyridine

(vi) R^4NH_2, PyBOP, HOBT, DIPEA, DMF

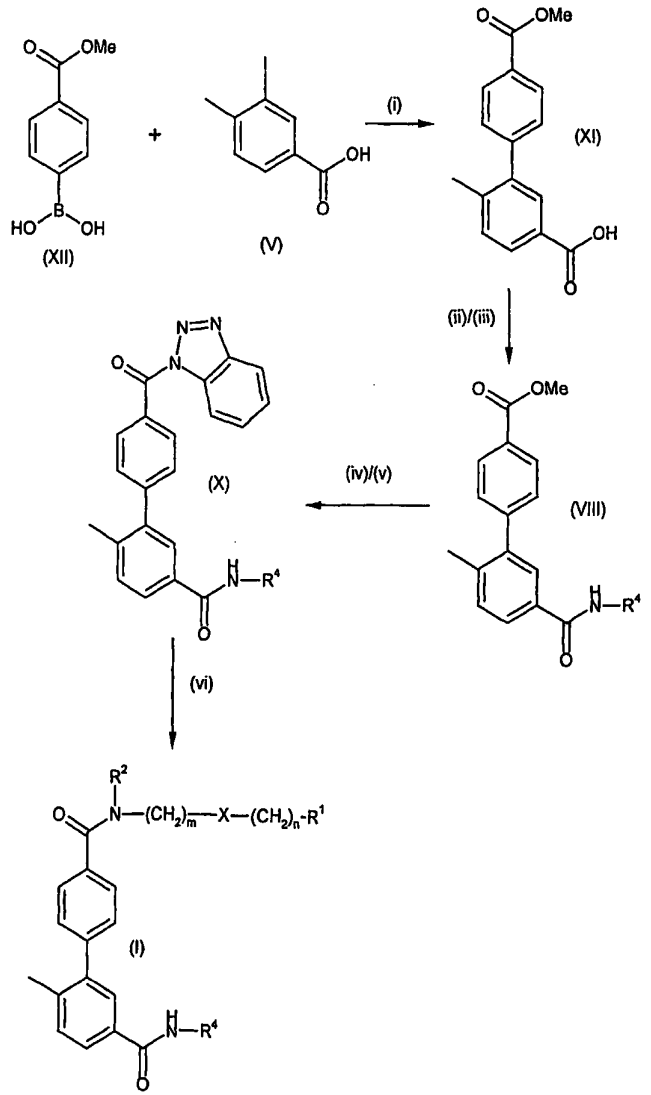
For example, a general method (B) for preparing the compounds of Formula (I) comprises the reactions set out in Scheme 2 below.



Scheme 2

(i) R^4NH_2, HATU, HOBT, DIPEA, DMF
(ii) (4-Methoxycarbonylphenyl)boronic acid, $(Ph_3P)_4Pd$, Na_2CO_3, DME
(iii) NaOH, MeOH, H_2O
(iv) $R^1(CH_2)_nX(CH_2)_mN\ R^2H$, HATU, HOBT, DIPEA, THF

For example, a general method (C) for preparing the compounds of Formula (I) comprises the reactions set out in Scheme 3 below.

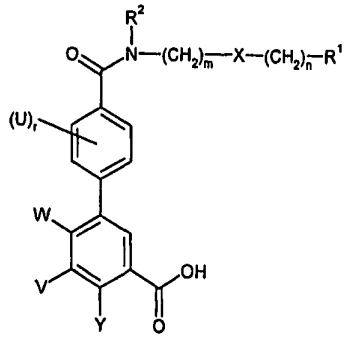


Scheme 3

(i) $CsCO_3$, $(Ph_3P)_4Pd$, DME
(ii) $(COCl)_2$, $CHCl_3$
(iii) R^4NH_2
(iv) NaOH, MeOH, H_2O
(v) 1-methylsulphonylbenzotriazole, Et_3N, THF, DMF
(vi) $R^1(CH_2)_nX(CH_2)_mN\ R^2H$, THF

Thus, according to the invention there is provided a process for preparing a compound of formula (I) which comprises:

(a) reacting a compound of formula (XIII)



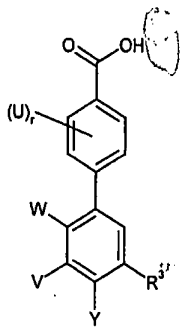
(XIII)

wherein R^1, R^2, X, U, W, V, Y, m, n and r are as defined above, with a compound of formula (XIV)

$$R^4\text{-}(CH_2)_q\text{-}NH_2 \quad \text{(XIV)}$$

wherein R^4 and q are as defined above, under amide forming conditions (if desired, the acid compound (XIII) may be converted to an activated form of the acid, for example the acid chloride, by treatment with, for example, oxalyl chloride, and then the activated acid thus formed reacted with the amine compound (XIV));

(b) reacting a compound of formula (XV)



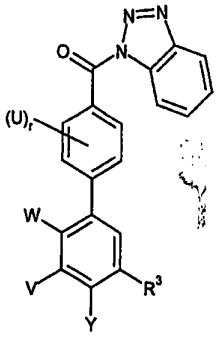
(XV)

wherein R^3, U, W, V, Y and r are as defined above, with a compound of formula (XVI)

$$R^1(CH_2)_nX(CH_2)_mNR^2H \quad \text{(XVI)}$$

wherein R^1, R^2, X, m and n are as defined above, under amide forming conditions;

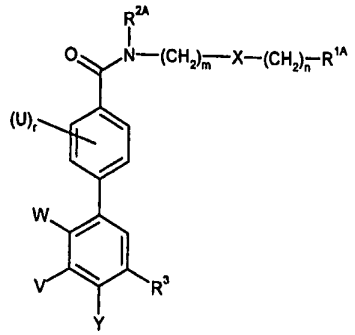
(c) reacting a compound of formula (XVII)



(XVII)

wherein R^3, U, W, V, Y and r are as defined above, with a compound of formula (XVI) as defined above; or

(d) functional group conversion of a compound of formula (XVIII)



(XVIII)

wherein R^3, X, U, W, V, Y, m, n and r are as defined above and R^{1A} and R^{2A} are R^1 and R^2 as defined above or groups convertible to R^1 and R^2,
to give a compound of formula (I).

Suitable amide forming conditions are well known in the art and include treating a solution of the acid, in for example THF, with an amine in the presence of, for example, HOBT, HATU and DIPEA.

Whilst it is possible for the compounds, salts or solvates of the present invention to be administered as the new chemical, the compounds of formula (I) and their pharmaceutically acceptable salts and solvates are conveniently administered in the form of pharmaceutical compositions. Thus, in another aspect of the invention, we provide a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, in admixture with one or more pharmaceutically acceptable carriers, diluents or excipients.

The compounds of formula (I) and their pharmaceutically acceptable salts and solvates may be formulated for administration in any suitable manner. They may, for example, be formulated for topical administration or administration by inhalation or, more preferably, for oral, transdermal or parenteral administration. The pharmaceutical composition may be in a form such that it can effect controlled release of the compounds of formula (I) and their pharmaceutically acceptable salts and solvates. A particularly preferred method of administration, and corresponding formulation, is oral administration.

For oral administration, the pharmaceutical composition may take the form of, and be administered as, for example, tablets (including sub-lingual tablets) and capsules (each including timed release and sustained release formulations), pills,

powders, granules, elixirs, tinctures, emulsions, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules can be made by preparing a powder mixture as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be

provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additives such as peppermint oil or saccharin, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of the present invention can also be administered in the form of liposome emulsion delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

The present invention includes pharmaceutical compositions containing 0.1 to 99.5%, more particularly, 0.5 to 90% of a compound of the formula (I) in combination with a pharmaceutically acceptable carrier.

Likewise, the composition may also be administered in nasal, ophthalmic, otic, rectal, topical, intravenous (both bolus and infusion), intraperitoneal, intraarticular, subcutaneous or intramuscular, inhalation or insufflation form, all using forms well known to those of ordinary skill in the pharmaceutical arts.

For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch.

For parenteral administration, the pharmaceutical composition may be given as an injection or a continuous infusion (e.g. intravenously, intravascularly or subcutaneously). The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. For administration by injection these may take the form of a unit dose presentation or as a multidose presentation preferably with an added preservative. Alternatively for parenteral administration the active ingredient may be in powder form for reconstitution with a suitable vehicle.

The compounds of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

Alternatively the composition may be formulated for topical application, for example in the form of ointments, creams, lotions, eye ointments, eye drops, ear drops, mouthwash, impregnated dressings and sutures and aerosols, and may contain appropriate conventional additives, including, for example, preservatives, solvents to assist drug penetration, and emollients in ointments and creams. Such topical formulations may also contain compatible conventional carriers, for example cream or ointment bases, and ethanol or oleyl alcohol for lotions. Such carriers may constitute from about 1% to about 98% by weight of the formulation; more usually they will constitute up to about 80% by weight of the formulation.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, tetrafluoroethane, heptafluoropropane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

The pharmaceutical compositions generally are administered in an amount effective for treatment or prophylaxis of a specific condition or conditions. Initial dosing in human is accompanied by clinical monitoring of symptoms, such symptoms for the selected condition. In general, the compositions are administered in an amount of active agent of at least about 100 µg/kg body weight. In most cases they will be administered in one or more doses in an amount not in excess of about 20 mg/kg body weight per day. Preferably, in

most cases, dose is from about 100 µg/kg to about 5 mg/kg body weight, daily. For administration particularly to mammals, and particularly humans, it is expected that the daily dosage level of the active agent will be from 0. 1 mg/kg to 10 mg/kg and typically around 1 mg/kg. It will be appreciated that optimum dosage will be determined by standard methods for each treatment modality and indication, taking into account the indication, its severity, route of administration, complicating conditions and the like. The physician in any event will determine the actual dosage which will be most suitable for an individual and will vary with the age, weight and response of the particular individual. The effectiveness of a selected actual dose can readily be determined, for example, by measuring clinical symptoms or standard anti-inflammatory indicia after administration of the selected dose. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention. For conditions or disease states as are treated by the present invention, maintaining consistent daily levels in a subject over an extended period of time, e.g., in a maintenance regime, can be particularly beneficial.

In another aspect, the present invention provides a compound of formula (I) or a salt or solvate thereof, for use in therapy.

The compounds of the present invention are generally inhibitors of the serine/threonine kinase p38 and are therefore also inhibitors of cytokine production which is mediated by p38 kinase. Within the meaning of the term "inhibitors of the serine/threonine kinase p38" are included those compounds that interfere with the ability of p38 to transfer a phosphate group from ATP to a protein substrate according to the assay described below.

It will be appreciated that the compounds of the invention may be selective for one or more of the isoforms of p38, for example p38α, p38β, p38γ and/or p38δ. In one embodiment, the compounds of the invention selectively inhibit the p38α isoform. In another embodiment, the compounds of the invention selectively inhibit the p38β isoform. In a further embodiment, the compounds of the invention selectively inhibit the p38α and p38β isoforms. Assays for determining the selectivity of compounds for the p38 isoforms are described in, for example, WO 99/61426, WO 00/71535 and WO 02/46158.

It is known that p38 kinase activity can be elevated (locally or throughout the body), p38 kinase can be incorrectly temporally active or expressed, p38 kinase can be expressed or active in an inappropriate location, p38 kinase can be constitutively expressed, or p38 kinase expression can be erratic; similarly, cytokine production mediated by p38 kinase activity can be occurring at inappropriate times, inappropriate locations, or it can occur at detrimentally high levels.

Accordingly, the present invention provides a method for the treatment of a condition or disease state mediated by p38 kinase activity, or mediated by cytokines produced by the activity of p38 kinase, in a subject which comprises administering to

said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof. The compound may be administered as a single or polymorphic crystalline form or forms, an amorphous form, a single enantiomer, a racemic mixture, a single stereoisomer, a mixture of stereoisomers, a single diastereoisomer or a mixture of diastereoisomers.

The present invention also provides a method of inhibiting cytokine production which is mediated by p38 kinase activity in a subject, e.g. a human, which comprises administering to said subject in need of cytokine production inhibition a therapeutic, or cytokine-inhibiting, amount of a compound of the present invention. The compound may be administered as a single or polymorphic crystalline form or forms, an amorphous form, a single enantiomer, a racemic mixture, a single stereoisomer, a mixture of stereoisomers, a single diastereoisomer or a mixture of diastereoisomers.

The present invention treats these conditions by providing a therapeutically effective amount of a compound of this invention. By "therapeutically effective amount" is meant a symptom-alleviating or symptom-reducing amount, a cytokine-reducing amount, a cytokine-inhibiting amount, a kinase-regulating amount and/or a kinase-inhibiting amount of a compound. Such amounts can be readily determined by standard methods, such as by measuring cytokine levels or observing alleviation of clinical symptoms. For example, the clinician can monitor accepted measurement scores for anti-inflammatory treatments.

The compounds of the present invention can be administered to any subject in need of inhibition or regulation of p38 kinase or in need of inhibition or regulation of p38 mediated cytokine production. In particular, the compounds may be administered to mammals. Such mammals can include, for example, horses, cows, sheep, pigs, mice, dogs, cats, primates such as chimpanzees, gorillas, rhesus monkeys, and, most preferably, humans.

Thus, the present invention provides methods of treating or reducing symptoms in a human or animal subject suffering from, for example, rheumatoid arthritis, osteoarthritis, asthma, psoriasis, eczema, allergic rhinitis, allergic conjunctivitis, adult respiratory distress syndrome, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, silicosis, endotoxemia, toxic shock syndrome, inflammatory bowel disease, tuberculosis, atherosclerosis, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, epilepsy, multiple sclerosis, aneurism, stroke, irritable bowel syndrome, muscle degeneration, bone resorption diseases, osteoporosis, diabetes, reperfusion injury, graft vs. host reaction, allograft rejections, sepsis, systemic cachexia, cachexia secondary to infection or malignancy, cachexia secondary to aquired immune deficiency syndrome (AIDS), malaria, leprosy, infectious arthritis, leishmaniasis, Lyme disease, glomerulonephritis, gout, psoriatic arthritis, Reiter's syndrome, traumatic arthritis, rubella arthritis, Crohn's disease, ulcerative colitis, acute synovitis, gouty arthritis, spondylitis,

and non articular inflammatory conditions, for example, herniated/ruptured/prolapsed intervertebral disk syndrome, bursitis, tendonitis, tenosynovitis, fibromyalgic syndrome and other inflammatory conditions associated with ligamentous sprain and regional musculoskeletal strain, pain, for example that associated with inflammation and/or trauma, osteopetrosis, restenosis, thrombosis, angiogenesis, cancer including breast cancer, colon cancer, lung cancer or prostatic cancer, which comprises administering to said subject a therapeutically effective amount of a compound of formula(I) or a pharmaceutically acceptable salt or solvate thereof.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from rheumatoid arthritis, asthma, psoriasis, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, systemic cachexia, glomerulonephritis, Crohn's disease, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, epilepsy and cancer including breast cancer, colon cancer, lung cancer and prostatic cancer, which comprises administering to said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from rheumatoid arthritis, asthma, psoriasis, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, systemic cachexia, glomerulonephritis, Crohn's disease and cancer including breast cancer, colon cancer, lung cancer and prostatic cancer, which comprises administering to said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from rheumatoid arthritis, neurodegenerative disease, Alzheimer's disease, Parkinson's disease and epilepsy which comprises administering to said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from any type of pain including chronic pain, rapid onset of analgesis, neuromuscular pain, headache, cancer pain, acute and chronic inflammatory pain associated with osteoarthritis and rheumatoid arthritis, post operative inflammatory pain, neuropathic pain, diabetic neuropathy, trigeminal neuralgia, post-hepatic neuralgia, inflammatory neuropathies and migraine pain which comprises administering to said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

A further aspect of the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for the treatment of a condition or disease state mediated by p38 kinase activity or mediated by cytokines produced by p38 kinase activity.

A further aspect of the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for the treatment of a condition or disease state selected from rheumatoid arthritis, osteoarthritis, asthma, psoriasis, eczema, allergic rhinitis, allergic conjunctivitis, adult respiratory distress syndrome, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, silicosis, endotoxemia, toxic shock syndrome, inflammatory bowel disease, tuberculosis, atherosclerosis, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, epilepsy, multiple sclerosis, aneurism, stroke, irritable bowel syndrome, muscle degeneration, bone resorption diseases, osteoporosis, diabetes, reperfusion injury, graft vs. host reaction, allograft rejections, sepsis, systemic cachexia, cachexia secondary to infection or malignancy, cachexia secondary to aquired immune deficiency syndrome (AIDS), malaria, leprosy, infectious arthritis, leishmaniasis, Lyme disease, glomerulonephritis, gout, psoriatic arthritis, Reiter's syndrome, traumatic arthritis, rubella arthritis, Crohn's disease, ulcerative colitis, acute synovitis, gouty arthritis, spondylitis, and non articular inflammatory conditions, for example, herniated/ruptured/prolapsed intervertebral disk syndrome, bursitis, tendonitis, tenosynovitis, fibromyalgic syndrome and other inflammatory conditions associated with ligamentous sprain and regional musculoskeletal strain, pain, for example that associated with inflammation and/or trauma, osteopetrosis, restenosis, thrombosis, angiogenesis, and cancer including breast cancer, colon cancer, lung cancer or prostatic cancer.

A further aspect of the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for the treatment of a condition or disease state selected from rheumatoid arthritis, asthma, psoriasis, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, systemic cachexia, glomerulonephritis, Crohn's disease, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, epilepsy, and cancer including breast cancer, colon cancer, lung cancer and prostatic cancer.

A further aspect of the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for the treatment of a condition or disease state selected from rheumatoid arthritis, asthma, psoriasis, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, systemic cachexia, glomerulonephritis, Crohn's disease and cancer including breast cancer, colon cancer, lung cancer and prostatic cancer.

A further aspect of the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for the treatment of a condition or disease state selected from rheumatoid

arthritis, neurodegenerative disease, Alzheimer's disease, Parkinson's disease and epilepsy.

A further aspect of the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for the treatment of any type of pain including chronic pain, rapid onset of analgesis, neuromuscular pain, headache, cancer pain, acute and chronic inflammatory pain associated with osteoarthritis and rheumatoid arthritis, post operative inflammatory pain, neuropathic pain, diabetic neuropathy, trigeminal neuralgia, post-hepatic neuralgia, inflammatory neuropathies and migraine pain.

The compounds of formula (I) and their salts, solvates and physiologically functional salts and solvates may be employed alone or in combination with other therapeutic agents for the treatment of the above-mentioned conditions. In particular, in rheumatoid arthritis therapy, combination with other chemotherapeutic or antibody agents is envisaged. Combination therapies according to the present invention thus comprise the administration of at least one compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof and at least one other pharmaceutically active agent. The compound(s) of formula (I) or pharmaceutically acceptable salt(s) or solvate(s) thereof and the other pharmaceutically active agent(s) may be administered together or separately and, when administered separately, this may occur separately or sequentially in any order. The amounts of the compound(s) of formula (I) or pharmaceutically acceptable salt(s) or solvate(s) thereof and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. Examples of other pharmaceutically active agents which may be employed in combination with compounds of formula (I) and their salts and solvates for rheumatoid arthritis therapy include: immunosuppresants such as amtolmetin guacil, mizoribine and rimexolone; anti-TNFα agents such as etanercept, infliximab, diacerein; tyrosine kinase inhibitors such as leflunomide; kallikrein antagonists such as subreum; interleukin 11 agonists such as oprelvekin; interferon beta 1 agonists; hyaluronic acid agonists such as NRD-101 (Aventis); interleukin 1 receptor antagonists such as anakinra; CD8 antagonists such as amiprilose hydrochloride; beta amyloid precursor protein antagonists such as reumacon; matrix metalloprotease inhibitors such as cipemastat and other disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate, sulphasalazine, cyclosporin A, hydroxychoroquine, auranofin, aurothioglucose, gold sodium thiomalate and penicillamine.

Examples

The following examples are illustrative embodiments of the invention, not limiting the scope of the invention in any way. Reagents are commercially available or are prepared according to procedures in the literature.

LCMS was conducted on a column (3.3cm x 4.6mm ID, 3um ABZ+PLUS), at a Flow Rate of 3ml/min, Injection Volume of 5µl, at room temperature and UV Detection Range at 215 to 330nm.

General Method A:

Benzoic acid (0.17mmol), HATU (0.2mmol), HOBT (0.17mmol), DIPEA (0.51mmol), and amine (0.2mmol) were mixed in DMF (2ml) and the reaction stirred at room temperature for 24h. Further portions of amine (0.05mmol) and HATU (0.052mmol) were added and the mixture heated for 18h at 60°C. The solvent was evaporated under vacuum and the residue partitioned between DCM (5ml) and aqueous sodium carbonate (1M, 5ml). The organic phase was reduced to dryness under vacuum and the amide purified as specified in the example.

Example 1: N^3-Cyclopropyl-6-methyl-$N^{4'}$-(4-methylpiperazin-1-yl)-1,1'-biphenyl-3,4'-dicarboxamide

a) N^3-Cyclopropyl-6-methyl-$N^{4'}$-(4-methylpiperazin-1-yl)-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from 3'-[(cyclopropylamino]carbonyl]-6'-methyl-1,1'-biphenyl-4-yl)carboxylic acid and 1-methylpiperazine using method A. Purified by chromatography on an SPE (silica, 5g) eluting with a DCM/ethanol/ammonia gradient (500:8:1 to 40:8:1). NMR: δH [$^2H_6$] – DMSO 8.42,(1H, d), 7.75,(1H, dd), 7.69,(1H, d), 7.46,(2H, d), 7.43,(2H, d), 7.38,(1H, d), 3.62,(2H, b), 2.84,(1H, m), 2.32,(6H, b), 2.27,(3H, s), 2.20,(3H, s), 0.67,(2H, m), 0.55,(2H, m). LCMS: retention time 2.10min, MH^+378.

b) 3'-[(Cyclopropylamino]carbonyl]-6'-methyl-1,1'-biphenyl-4-yl)carboxylic acid

Methyl 3'-[(cyclopropylamino]carbonyl]-6'-methyl-1,1'-biphenyl-4-yl)carboxylate (2.7g, 8.7mmol) and lithium hydroxide monohydrate (0.77g, 18.3mmol) were mixed in THF (20ml) and water (10ml) and heated at 80°C for 2h. The THF was evaporated under vacuum and hydrochloric acid (2N) added to the aqueous with vigorous stirring. The solid produced was filtered off, dissolved in methanol and absorbed onto silica. Purified by flash column chromatography eluting with DCM/ethanol/ammonia (20:8:1). The product fractions were concentrated under vacuum to give 3'-[(cyclopropylamino]carbonyl]-6'-methyl-1,1'-biphenyl-4-yl)carboxylic acid (2.0g, 78%). LCMS: retention time 2.94min, MH^+ 296.

c) Methyl 3'-[(cyclopropylamino]carbonyl]-6'-methyl-1,1'-biphenyl-4-yl)carboxylate

N-Cyclopropyl-3-iodo-4-methylbenzamide (4.7g, 15.6mmol), (4-methoxycarbonylphenyl)boronic acid (3.4g, 18.7mmol), aqueous sodium carbonate (1M, 50ml) and tetrakis(triphenylphosphine)palladium (1.8g, 0.156mmol) in DME (100ml) were heated at 95°C for 18h. The reaction mixture was absorbed onto silica and purified by flash column chromatography eluting with DCM/ethanol/ammonia (500:8:1).

The product fractions were reduced to dryness under vacuum to give methyl 3'-[(cyclopropylamino]carbonyl]-6'-methyl-1,1'-biphenyl-4-yl)carboxylate (2.76g, 57%).
LCMS: retention time 3.21min, MH^+ 310.

d) N-Cyclopropyl-3-iodo-4-methylbenzamide

3-Iodo-4-methylbenzoic acid (5g, 19.1mmol) and HATU (8.71g, 22.9mmol) in DMF (25ml) were stirred at room temperature for 10minutes. HOBT (2.58g, 19.1mmol), cyclopropylamine (1.37g, 22.9mmol) and DIPEA (2.5ml, 57.3mmol) were added and stirring continued for 18h. The DMF was evaporated under vacuum and the residue partitioned between DCM (100ml) and aqueous sodium carbonate (1M, 75ml). The aqueous layer was extracted with DCM (50ml) and the combined organic phases washed with brine (75ml) and dried (magnesium sulphate). The solution was absorbed onto silica and purified by chromatography on silica eluting with ethyl acetate/cyclohexane (1:3). The product fractions were reduced to dryness under vacuum to give N-cyclopropyl-3-iodo-4-methylbenzamide (4.7g, 82%). LCMS: retention time 3.09min, MH^+ 302.

Example 2: N^3-Cyclopropyl-$N^{4'}$-(3-imidazol-1-ylpropyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

N^3-Cyclopropyl-$N^{4'}$-(3-imidazol-1-ylpropyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from 3'-[(cyclopropylamino]carbonyl]-6'-methyl-1,1'-biphenyl-4-yl)carboxylic acid and 1-(3-aminopropyl)imidazole using method A. Purified by chromatography on silica, eluting with a DCM/ethanol/ammonia gradient (200:8:1 to 75:8:1). NMR: δH [$^2H_6$] – DMSO 8.58,(1H, t), 8.43,(1H, d), 7.93,(2H, d), 7.75,(1H, dd), 7.68,(1H, d), 7.66,(1H, s), 7.47,(2H, d), 7.38,(1H, d), 7.21,(1H, s), 6.89,(1H, s), 4.03,(2H, t), 3.26,(2H, q), 2.83,(1H, m), 2.26,(3H, s), 1.97,(2H, m), 0.67,(2H, m), 0.55,(2H, m).
LCMS: retention time 2.20min, MH^+ 403.

Example 3: N^3-Cyclopropyl-6-methyl-$N^{4'}$-(3-morpholin-4-ylpropyl)-1,1'-biphenyl-3,4'-dicarboxamide

N^3-Cyclopropyl-6-methyl-$N^{4'}$-(3-morpholin-4-ylpropyl)-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from 3'-[(cyclopropylamino]carbonyl]-6'-methyl-1,1'-biphenyl-4-yl)carboxylic acid and 4-(3-aminopropyl)morpholine using method A. Purified by chromatography on silica, eluting with a DCM/ethanol/ammonia gradient (200:8:1 to 75:8:1). NMR: δH [$^2H_6$] – DMSO 8.55,(1H, t), 8.42,(1H, d), 7.91,(2H, d), 7.74,(1H, dd), 7.68,(1H, d), 7.46,(2H, d), 7.38,(1H, d), 3.56,(4H, t), 3.30,(2H, m), 2.83,(1H, m), 2.34,(6H, m), 2.26,(3H, s), 1.69,(2H, m), 0.67,(2H, m), 0.54,(2H, m).
LCMS: retention time 2.28min, MH^+ 422.

Example 4: N^3-Cyclopropyl-6-methyl-$N^{4'}$-[3-(4-methylpiperazin-1-yl)propyl]-1,1'-biphenyl-3,4'-dicarboxamide

N^3-Cyclopropyl-6-methyl-$N^{4'}$-[3-(4-methylpiperazin-1-yl)propyl]-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from 3'-[(cyclopropylamino]carbonyl]-6'-methyl-1,1'-

biphenyl-4-yl)carboxylic acid and 1-(3-aminopropyl)-4-methylpiperazine using method A. Purified by chromatography on silica, eluting with a DCM/ethanol/ammonia gradient (100:8:1 to 40:8:1). NMR: δH [$^2H_6$] – DMSO 8.56,(1H, t), 8.42,(1H, d), 7.91,(2H, d), 7.74,(1H, dd), 7.68,(1H, d), 7.45,(2H, d), 7.38,(1H, d), 3.30,(2H, m), 2.83,(1H, m), 2.48-2.17,(13H, bm), 2.14,(3H, s), 1.68,(2H, m), 0.67,(2H, m), 0.54,(2H, m).
LCMS: retention time 2.2min, MH^+ 435.

Example 5: $N^{4'}$-(3-Imidazol-1-ylpropyl)-6-methyl-N^3-propyl-1,1'-biphenyl-3,4'-dicarboxamide

a) 5'-[(1H-1,2,3-Benzotriazol-1-yl)carbonyl]-2'-methyl-N-propyl-1,1'-biphenyl-3-carboxamide (25mg, 0.062mmol) in THF (1ml) was mixed with 1-(3-aminopropyl)imidazole (7.2µl) in THF (0.6ml) and the reaction stirred at room temperature for 4h. The reaction was loaded onto an SPE (aminopropyl, 1g) and eluted with chloroform, ethyl acetate and methanol. The methanol fraction was applied to an SPE (SCX, 0.5g), washed with methanol and eluted with methanol/ammonia. The solvent was evaporated from the methanol/ammonia fractions to give $N^{4'}$-(3-imidazol-1-ylpropyl)-6-methyl-N^3-propyl-1,1'-biphenyl-3,4'-dicarboximide. NMR: δH $CDCl_3$ 7.82,(2H, d), 7.67,(1H, dd), 7.62,(1H, d), 7.47,(1H, s), 7.40,(1H, t), 7.32-7.28,(3H, m), 7.03,(1H, s), 6.97,(1H, s), 6.70,(1H, t), 4.05,(2H, m), 3.48,(2H, q), 3.39,(2H, q), 2.12,(2H, m), 1.62,(2H, m), 0.96,(3H, t). LCMS: retention time 2.33min, MH^+ 405.

b) 4'-[(1H-1,2,3-Benzotriazol-1-yl)carbonyl]-6-methyl-N-propyl-1,1'-biphenyl-3-carboxamide

6'-Methyl-3'-[(propylamino)carbonyl]-1,1'-biphenyl-4-carboxylic acid (121mg, 0.41mmol), triethylamine (100µl) and 1-(methylsulphonyl)-1H-benzotriazole (119mg, 0.6mmol) were mixed in THF (3ml) and DMF (0.5ml) and heated at reflux for 3h. The reaction was concentrated under vacuum and partitioned between chloroform (5ml) and water (5ml). The aqueous was washed with chloroform (3ml) and the combined organics reduced to dryness under vacuum. The residue was chromatographed on an SPE (silica, 5g) eluting with chloroform, ether and ethylacetate, which after evaporation of the solvent under vacuum gave 4'-[(1H-1,2,3-benzotriazol-1-yl)carbonyl]-6-methyl-N-propyl-1,1'-biphenyl-3-carboxamide (150mg).

c) 6'-Methyl-3'-[(propylamino)carbonyl]-1,1'-biphenyl-4-carboxylic acid

Methyl 6'-methyl-3'-[(propylamino)carbonyl]-1,1'-biphenyl-4-carboxylate (216mg, 0.7mmol) in methanol (4ml) was mixed with aqueous sodium hydroxide (2N, 1ml) and stirred at room temperature for 2h. The methanol was evaporated, the reaction diluted with water (4ml) and extracted with chloroform (2x 5ml). The aqueous was acidified with hydrochloric acid (2N, 2ml) and extracted with chloroform (2x 6ml). Both sets of organic extracts were combined in methanol (4ml) and stirred with aqueous sodium hydroxide (2N, 2ml) for 3h. The methanol was evaporated, the reaction diluted with water (4ml) and washed with chloroform (2x 5ml). The aqueous was acidified with hydrochloric acid (2N, 2ml) and extracted with chloroform (2x 6ml). The solvent was

evaporated from the organic extracts to give 6'-methyl-3'-[(propylamino)carbonyl]-1,1'-biphenyl-4-carboxylic acid (121mg). NMR: δH $CDCl_3$ 8.13,(2H, d), 7.69,(1H, dd), 7.62,(1H, d), 7.41,(2H, d), 7.35,(1H, d), 3.42,(2H, t), 2.30,(3H, s), 1.64,(2H, m), 0.99,(3H, t).

d) Methyl 6'-methyl-3'-[(propylamino)carbonyl]-1,1'-biphenyl-4-carboxylate

4'-(Methoxycarbonyl)-6-methyl-1,1'-biphenyl-3-carboxylic acid (190mg, 0.7mmol) and oxalyl chloride (70µl, 0.77mol) in chloroform (4ml) were stirred at room temperature for 15min. Propylamine (200µl) was added and stirring continued for 45min. The reaction was quenched with water (4ml), the phases separated and the organic phase passed through an aminopropyl SPE eluting with chloroform. After evaporation of the solvent this gave methyl 6'-methyl-3'-[(propylamino)carbonyl]-1,1'-biphenyl-4-carboxylate (216mg). LCMS: retention time 3.26min, MH^+ 312.

e) 4'-(Methoxycarbonyl)-6-methyl-1,1'-biphenyl-3-carboxylic acid

3-Iodo-4-methylbenzoic acid (8.7g, 33.3mmol), (4-methoxycarbonylphenyl)boronic acid (6.0g, 33.3mmol), caesium carbonate (10.8g, 33.3mmol) and tetrakis(triphenylphosphine)palladium (1.92g, 1.67mmol) in DME (120ml) were heated at 90°C for 6h. The cooled reaction mixture was filtered and the residue washed with DME. The combined filtrate and washings were absorbed onto silica and chromatographed on a silica flash column eluting with DCM/ethanol/ ammonia (40:8:1 then 30:8:1). The product fractions were reduced to dryness under vacuum to give 4'-(methoxycarbonyl)-6-methyl-1,1'-biphenyl-3-carboxylic acid (2.28g, 25%). LCMS: retention time 3.22min, $[M-H]^-$ 269.

f) 1-(Methylsulphonyl)-1H-benzotriazole

Methanesulphonyl chloride (9.3ml, 0.12mol) in toluene (30ml) was added dropwise to a solution of benzotriazole (11.9g, 0.1mol) and pyridine (12ml, 0.16mol) in toluene (120ml). The reaction was stirred at room temperature for 20h, diluted with ethyl acetate (150ml), washed with water (2x 100ml), brine (150ml) and dried (magnesium sulphate). The solvent was evaporated under vacuum to give 1-(methylsulphonyl)-1H-benzotriazole (19g). NMR: δH $CDCl_3$ 8.17,(1H, m), 8.02,(1H, m), 7.69,(1H, m), 7.55,(1H, m), 3.52,(3H, s).

Example 6: N^3-Cyclopropyl-6-methyl-$N^{4'}$-[4-(4-methylpiperazin-1-yl)benzyl]-1,1'-biphenyl-3,4'-dicarboxamide

Example 7: N^3-Cyclopropyl-6-methyl-$N^{4'}$-(1,3-thiazol-2-ylmethyl)-1,1'-biphenyl-3,4'-dicarboxamide

Example 8: N^3-Cyclopropyl-6-methyl-$N^{4'}$-{3-[(4-methylpiperazin-1-yl)methyl]phenyl}-1,1'-biphenyl-3,4'-dicarboxamide

General Method B:

HATU (65mg, 0.17mmol) was added to a solution of {3'-[(cyclopropylcarbonyl)amino]-6'-methyl-biphen-4-yl}carboxylic acid (50mg, 0.17mmol) in DMF (2ml). After 5 minutes HOBT (23mg, 0.17mmol), the chosen amine (0.17mmol) and DIPEA (0.087ml, 0.51mmol) were added and the reaction mixture stirred at room temperature under nitrogen for 18 hours. The DMF was removed *in vacuo* and the residue partitioned between DCM (5ml) and aqueous sodium carbonate (1M, 5ml). The layers were separated and the organic layer purified by SPE cartridge (SI, 5g) eluting in turn with DCM, chloroform, ether, ethyl acetate, acetonitrile, acetone, ethanol and DCM:ethanol:ammonia (40:8:1, 20:8:1, 10:8:1) to give the desired products.

Compound	Amine	MH^+	Retention time (minutes)
Example 6	1-methyl-4-(4-aminomethyl-phenyl)piperazine	483	2.37
Example 7	2-aminomethylthiazole	392	2.88
Example 8	1-(3-aminobenzyl)-4-methyl-piperazine	483	2.50

Example 9: N^3-Cyclopropyl-5-fluoro-6-methyl-$N^{4'}$-[3-(morpholin-4-ylmethyl)benzyl]-1,1'-biphenyl-3,4'-dicarboxamide

{3'-[(Cyclopropylamino)carbonyl]-5'-fluoro-6'-methyl-1,1'-biphen-4-yl}carboxylic acid (Intermediate 1, 31mg, 0.10mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (21mg, 0.11mmol), HOBT (15mg, 0.11mmol) and 4-(3-aminomethylbenzyl)morpholine (Intermediate 3, 0.11mmol) were dissolved in DMF (4ml). DIPEA (19µl, 0.11mmol) was added to the solution which was then stirred for 5 hours at 40°C. Ethyl acetate (25ml) and water (25ml) were added. The ethyl acetate layer was separated and washed sequentially with saturated sodium hydrogen carbonate and hydrochloric acid (0.5M). The solvent was removed *in vacuo* and the residue was purified by mass-directed HPLC to give N^3-cyclopropyl-5-fluoro-6-methyl-$N^{4'}$-[3-(morpholin-4-ylmethyl)benzyl]-1,1'-biphenyl-3,4'-dicarboxamide.
LCMS: MH^+ 502, 3.02minutes.

(a) {3'-[(Cyclopropylamino)carbonyl]-5'-fluoro-6'-methyl-1,1'-biphen-4-yl}carboxylic acid (Intermediate 1)

3-Bromo-N-cyclopropyl-5-fluoro-4-methylbenzamide (Intermediate 2, 120mg, 0.45mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (111mg, 0.45mmol) and tetrakis(triphenylphosphine) palladium (51mg, 0.045mmol) were dissolved in DME (3ml) and aqueous sodium carbonate (1M, 450µl) was added. The

mixture was refluxed at 80°C for 16 hours. Solvent was removed *in vacuo* and the residue was purified by silica biotage chromatography, eluting with 2:1 ethyl acetate:cyclohexane followed by 9:1 ethyl acetate:methanol. To give {3'-[(cyclopropylamino)carbonyl]-5'-fluoro-6'-methyl-1,1'-biphen-4-yl}carboxylic acid (129mg, 91%).
LCMS: MH^+ 314, retention time 3.06 min.

(b) 3-Bromo-N-cyclopropyl-5-fluoro-4-methylbenzamide (Intermediate 2)

3-Fluoro-4-methylbenzoic acid (462mg, 3.0mmol) was added to a stirred mixture of bromine (2.31ml, 45mmol) and iron powder (252mg, 4.5mmol) under nitrogen. The reaction was stirred at 20°C for 4 hours and then left to stand for 16 hours. Sodium thiosulphate solution (200ml) was added and the product was extracted into ethyl acetate (3 x 150ml). Ethyl acetate extracts were combined and evaporated *in vacuo*. The crude product (mixture of isomers) was dissolved in DMF (7ml). Cyclopropylamine (208µl, 3.0mmol), HOBT (405mg, 3.0mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (575mg, 3.0mmol) and DIPEA (525µl, 3.0mmol) were added to the stirred solution. The reaction was stirred for 5 hours at 20°C. Solvent was removed *in vacuo* and the residue was partitioned between ethyl acetate and water. Combined ethyl acetate extracts were washed sequentially with aqueous sodium hydrogen carbonate and hydrochloric acid (0.5M), then dried (magnesium sulphate). The ethyl acetate was evaporated *in vacuo* and the residue was purified by silica biotage chromatography eluting with cyclohexane:ethyl acetate (6:1)to give 3-bromo-N-cyclopropyl-5-fluoro-4-methylbenzamide (359mg, 44%).
NMR: δH – $CDCl_3$ 7.68,(1H, s), 7.39,(1H, d), 6.19,(1H, bs), 2.88,(1H, m), 2.36,(3H, d), 0.88,(2H, m), 0.63,(2H, m). LCMS: MH^+ 272/274, retention time 3.12 min.

(c) 4-(3-Aminomethylbenzyl)morpholine (Intermediate 3)

A solution of N-tert-butyloxycarbonyl-3-(4-morpholinylmethylbenzyl)-carbamic acid tert-butyl ester (Intermediate 4, 1.8g) in hydrogen chlorine in dioxane (4N) was stirred at room temperature for 2hours.The solvent was evaporated under vacuum and the residue partitioned between water (10ml) and ethyl acetate (10ml). The organic phase was extracted with water (5ml) and the combined aqueous phases basified with sodium hydroxide (2N). The aqueous was extracted with ethyl acetate (3x 10ml) and the organic extracts combined, dried (magnesium sulphate) and the solvent evaporated *in vacuo* to give 3-(4-morpholinylmethyl)benzylamine (370mg).
NMR; δH – $CDCl_3$ 7.44-7.16,(4H, m), 3.93-3.46,(8H, m), 2.47,(4H, m). MS: MH^+ 207.

(d) N-tert-Butyloxycarbonyl-3-(4-morpholinylmethylbenzyl)-carbamic acid tert-butyl ester (Intermediate 4)

Morpholine (2.3ml) was added to a solution of (3-chloromethyl-benzyl)-carbamic acid *tert*-butyl ester (Intermediate 5, 1.7g) in THF (20ml) and the mixture heated at reflux under nitrogen for 6hours. Concentration of the reaction under vacuum gave N-tert-butyloxycarbonyl-3-(4-morpholinylmethyl)benzylamine (1.94g).
NMR; δH – $CDCl_3$ 7.41-7.16,(4H, m), 4.91,(1H, b), 4.42,(2H, b), 3.72,(4H, m), 3.50,(2H, s), 2.45,(4H, m), 1.5,(9H, s). MS: MH^+ 307.

(e) (3-Chloromethylbenzyl)-carbamic acid *tert*-butyl ester (Intermediate 5)

Triethylamine (21.27ml, 152.6mmol) was added to a suspension of 3-chloromethylbenzylamine hydrochloride (Intermediate 6, 167.92mmol) in dry THF (180ml). A solution of di-tert-butyl dicarbonate (14.75g, 67.58mmol) in dry THF (50ml) was added dropwise at 0°C. Once the addition was complete, the reaction mixture was stirred at room temperature for 18 hours. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in ethyl acetate (250ml) and washed with water (150ml). The aqueous layer was extracted with ethyl acetate (50ml). The combined organic extracts were washed with cold hydrochloric acid (1N, 80ml), aqueous sodiumhydrogen carbonate solution (100ml), dried (magnesium sulphate), filtered and concentrated *in vacuo* to give (3-Chloromethylbenzyl)-carbamic acid *tert*-butyl ester (12g, 46.9mmol).
MS: MNH_4^+ 273.

(f) 3-Chloromethylbenzylamine hydrochloride (Intermediate 6)

Hexamethylenetriamine (27.13g, 0.194mol) was added to a solution of dichloro-m-xylene (34g, 0.194mol) in chloroform (230ml) and the mixture heated at reflux for 30minutes. The cooled reaction was filtered and the filtrate reduced to dryness under vacuum. The residue was dissolved in ethanol (340ml), treated with concentrated hydrochloric acid (32ml) and heated at reflux for 3hours. The reaction was reduced to 4ml under vacuum, diluted with ether (250ml) and filtered to give 3-chloromethylbenzylamine hydrochloride (10.57g).
MS: MH^+ 156.

Example 10: N^3-Cyclopropyl-6-methyl-$N^{4'}$-[3-(morpholin-4-ylmethyl)benzyl]-1,1'-biphenyl-3,4'-dicarboxamide

Example 11: N^3-Cyclopropyl-6-methyl-$N^{4'}$-[2-[(4-methylpiperazin-1-yl)methyl]phenyl]-1,1'-biphenyl-3,4'-dicarboxamide

Example 12: tert-Butyl 4-[[({5'-[(cyclopropylamino)carbonyl]-2'-methyl-1,1'-biphenyl-4-yl}carbonyl)amino]methyl]piperidine-1-carboxylate

Example 13: N^3-Cyclopropyl-6-methyl-$N^{4'}$-[2-(4-methylpiperazin-1-yl)phenyl]-1,1'-biphenyl-3,4'-dicarboxamide

Example 14: N^3-Cyclopropyl-6-methyl-$N^{4'}$-[3-(4-methylpiperazin-1-yl)phenyl]-1,1'-biphenyl-3,4'-dicarboxamide

General Method C:

HATU (65mg, 0.17mmol) was added to a solution of {3'-[(cyclopropylcarbonyl)amino]-6'-methyl-biphen-4-yl}carboxylic acid (50mg, 0.17mmol) in DMF (2ml). After 5 minutes HOBT (23mg, 0.17mmol), the amine (0.17mmol) and DIPEA (0.087ml, 0.51mmol) were added and the reaction mixture stirred at room temperature under nitrogen for 18 hours. The reaction was partitioned between ethyl acetate (50ml) and hydrochloric acid (1M, 50ml). The organic phase was washed with aqueous sodium carbonate (1M, 50ml) and brine (25ml), dried (magnesium sulphate), and the solvent removed *in vacuo*. The crude material was purified by Biotage cartidge (Si, 8g) eluting with a toluene:ethanol gradient (95:5 to 70:30) to yield the desired products.

Compound	Amine	MH^+	Retention time (minutes)
Example 10	4-(3-aminomethylbenzyl)morpholine	484	2.42
Example 11	1-(2-aminobenzyl)-4-methylpiperazine	483	2.43
Example 12	4-(aminomethyl)piperidine-1-carboxylic acid *tert*-butyl ester	492	3.31
Example 13	1-(2-aminophenyl)-4-methylpiperazine	469	2.44
Example 14	1-(3-aminophenyl)-4-methylpiperazine	469	2.41

Example 15: N^3-Cyclopropyl-6-methyl-$N^{4'}$-[3-(pyrrolidin-1-ylmethyl)benzyl]-1,1'-biphenyl-3,4'-dicarboxamide

Example 16: N^3-Cyclopropyl-6-methyl-$N^{4'}$-[3-[(4-methylpiperazin-1-yl)methyl]benzyl]-1,1'-biphenyl-3,4'-dicarboxamide

Example 17: N^3-Cyclopropyl-6-methyl-$N^{4'}$-[4-(morpholin-4-ylmethyl)benzyl]-1,1'-biphenyl-3,4'-dicarboxamide

Example 18: N^3-Cyclopropyl-6-methyl-$N^{4'}$-[4-[(4-methylpiperazin-1-yl)methyl]benzyl]-1,1'-biphenyl-3,4'-dicarboxamide

Example 19: N^3-Cyclopropyl-6-methyl-$N^{4'}$-(pyridin-4-ylmethyl)-1,1'-biphenyl-3,4'-dicarboxamide

Example 20: N^3-Cyclopropyl-6-methyl-$N^{4'}$-[4-(piperidin-1-ylmethyl)benzyl]-1,1'-biphenyl-3,4'-dicarboxamide

Example 21: N^3-Cyclopropyl-6-methyl-$N^{4'}$-[4-(pyrrolidin-1-ylmethyl)benzyl]-1,1'-biphenyl-3,4'-dicarboxamide

Example 22: N^3-Cyclopropyl-$N^{4'}$-[3-(1H-imidazol-1-ylmethyl)phenyl]-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 23: N^3-Cyclopropyl-6-methyl-$N^{4'}$-[3-(piperidin-1-ylmethyl)benzyl]-1,1'-biphenyl-3,4'-dicarboxamide

Example 24: N^3-Cyclopropyl-6-methyl-$N^{4'}$-(tetrahydrofuran-2-ylmethyl)-1,1'-biphenyl-3,4'-dicarboxamide

General Method D:

A solution of {3'-[(cyclopropylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid (50mg, 0.17mmol) in DMF (1ml) was treated with HATU (65mg, 0.17mmol) at room temperature. After 5minutes this was added to a solution of the amine (0.17mmol) and HOBT (23mg, 0.17mmol) in DMF (1ml). DIPEA (87ul, 3eq) was added. The reaction mixture was left at room temperature for 16hrs, then concentrated *in vacuo*. The residue was dissolved in DCM (1ml) and loaded onto a SPE cartridge (1g, aminopropyl) which had been pre-equilibrated with DCM. Residual sample was washed on with another portion of DCM (0.5ml) , The cartridge was then eluted with: DCM (1x2.5ml), chloroform (1x2.5ml), ethyl acetate (1x2.5ml), and methanol (1x2.5ml). The fractions containing product were isolated by evaporation to give the desired product.

Compound	Amine	MH^+	Retention time (minutes)
Example 15	1-(3-aminomethylbenzyl)pyrrolidine	468	2.48
Example 16	1-(3-aminomethylbenzyl)-4-methylpiperazine	-	2.44
Example 17	4-(4-aminomethylbenzyl)morpholine	484	2.42

Example 18	1-(4-aminomethylbenzyl)-4-methylpiperazine	497	2.42
Example 19	4-aminomethylpyridine	386	2.36
Example 20	1-(4-aminomethylbenzyl)piperidine	482	2.49
Example 21	1-(4-aminomethylbenzyl)pyrrolidine	468	2.45
Example 22	3-(1H-imidazol-1-ylmethyl)aniline	451	2.52
Example 23	1-(3-aminomethylbenzyl)piperidine	482	2.52
Example 24	2-(aminomethyl)tetrahydrofuran	379	2.85

Example 25: N^3-Cyclopropyl-$N^{4'}$-({5-[(dimethylamino)methyl]-2-furyl}methyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

HATU (65mg, 0.17mmol) was added to a solution of {3'-[(cyclopropylcarbonyl)amino]-6'-methyl-biphen-4-yl}carboxylic acid (50mg, 0.17mmol) in DMF (1ml). After 5 minutes HOBT (23mg, 0.17mmol), 2-aminomethyl-5-(dimethylaminomethyl)furan oxalic acid salt (68mg, 0.204mmol) and DIPEA (0.087ml, 0.51mmol) were added and the reaction mixture stirred at room temperature under nitrogen for 18 hours. The DMF was removed *in vacuo* and the residue partitioned between DCM (10ml) and aqueous sodium carbonate (1M, 10ml). The organic phase wwas reduced to dryness under vacuum and purified by SPE cartridge (Si, 10g) eluting in turn with DCM, ether, ethyl acetate, acetonitrile, acetone and ethanol to give the N^3-cyclopropyl-$N^{4'}$-({5-[(dimethylamino)methyl]-2-furyl}methyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide (35mg, 0.081mmol).

NMR: δH [$^2H_6$] – DMSO 9.05,(1H, bt,), 8.43,(1H, bd), 7.9, (2H, d) 7.77,(1H, dd), 7.70,(1H, d), 7.48,(2H, d), 7.39,(1H, d), 6.20,(2H, dd), 4.46,(2H, d), 3.36,(2H, s), 2.85,(1H, m), 2.27,(3H, s), 2.12,(6H, s), 0.72-0.52,(4H,2xm). LC/MS: MH^+ 432, retention time 2.31minutes.

Example 26: N^3-Cyclopropyl-6-methyl-$N^{4'}$-(piperidin-4-ylmethyl)-1,1'-biphenyl-3,4'-dicarboxamide

Trifluoroacetic acid (1ml) and 1 drop of water were added to tert-butyl 4-{[({5'-[(cyclopropylamino)carbonyl]-2'-methyl-1,1'-biphenyl-4-yl}carbonyl)amino]methyl}piperidine-1-carboxylate (19mg, 0.038mmol) and the solution stirred at room temperature under nitrogen for 1 hour. The trifluoroacetic acid was removed in vacuo and the residue partitioned between ethyl acetate (5ml) and aqueous

sodium carbonate (1M, 5ml). The layers were separated and the aqueous layer extracted with ethyl acetate (2x5ml). The organic extracts were washed with brine (10ml), dried (magnesium sulphate) and concentrated in vacuo to give N~3~-cyclopropyl-6-methyl-N~4~'-(piperidin-4-ylmethyl)-1,1'-biphenyl-3,4'-dicarboxamide (8mg, 0.020mmol).

NMR: δH [$^2H_6$] – DMSO 8.56,(1H, bt), 8.44,(1H, bd), 7.92,(2H, d) 7.77,(1H, dd), 7.69,(1H, d), 7.48,(2H, d), 7.39,(1H, d), 3.16,(2H, bt), 3.02,(2H, bdt), 2.84,(1H, m), 2.52,(2H, m), 2.28,(3H, s), 1.22-1.12,(3H, bm), 1.75-1.63,(3H,m + bd), 0.69-0.52,(4H, 2xm). LC/MS: MH^+ 392, retention time 2.26minutes.

Abbreviations

DCM	Dichloromethane
DIPEA	N,N-Diisopropylethylamine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulphoxide
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HBTU	O-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
HOBT	1-Hydroxybenzotriazole hydrate
PyBOP	Benzotriazol-1-yl-oxy-tripyrrolidinophosphonium hexafluorophosphate
SPE	Solid phase extraction
THF	Tetrahydrofuran

The activity of the compounds of the invention as p38 inhibitors may be demonstrated in the following assays:

p38 Kinase Assay

The peptide substrate used in the p38 assay was biotin-IPTSPITTTYFFFRRR-amide. The p38 and MEK6 proteins were purified to homogeneity from E.coli expression systems. The fusion proteins were tagged at the N-terminus with Glutathione-S-Transferase (GST). The maximum activation was achieved by incubating 20uL of a reaction mixture of 30nM MEK6 protein and 120nM p38 protein in the presence of 1.5uM peptide and 10mM $Mg(CH_3CO_2)_2$ in 100mM HEPES, pH 7.5, added to 15uL of a mixture of 1.5uM ATP with 0.08uCi [g-^{33}P]ATP, with or without 15uL of inhibitor in 6%DMSO. The controls were reactions in the presence (negative controls) or absence (positive controls) of 50 mM EDTA. Reactions were allowed to proceed for 60 min at room temperature and quenched with addition of 50uL of 250mM EDTA and

mixed with 150uL of Streptavidin SPA beads (Amersham) to 0.5mg/reaction. The Dynatech Microfluor white U-bottom plates were sealed and the beads were allowed to settle overnight. The plates were counted in a Packard TopCount for 60 seconds. IC_{50} values were obtained by fitting raw data to %I = 100*(1-(I-C2)/(C1-C2)), where I was CPM of background, C1 was positive control, and C2 was negative control.

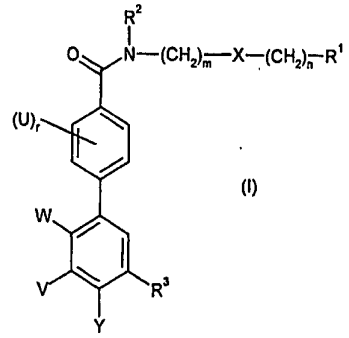
α P38 Fluorescence Polarisation Method

αP38 was prepared in house. SB4777790-R Ligand was diluted in HEPES containing $MgCl_2$, CHAPS, DTT and DMSO. This was added to blank wells of a Black NUNC 384 well plate. αP38 was added to this ligand mixture then added to the remainder of the 384 well plate containing controls and compounds. The plates were read on an LJL Analyst and Fluorescence Anisotropy used to calculate the compound inhibition

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process or use claims and may include, by way of example and without limitation, one or more of the following claims:

Claims:

1. A compound of formula (I):



(I)

wherein

X is a bond or a phenyl group which may be optionally substituted;

R^1 is selected from an optionally substituted five- to seven-membered heterocyclic ring, an optionally substituted five- to seven-membered heteroaryl ring and an optionally substituted fused bicyclic ring;

R^2 is selected from hydrogen, C_{1-6}alkyl and $-(CH_2)_p-C_{3-7}$cycloalkyl;

or when X is a bond and m and n are both zero, R^1 and R^2, together with the nitrogen atom to which they are bound, form a five- to six-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen and nitrogen, which can be optionally substituted by C_{1-4}alkyl;

R^3 is the group $-CO-NH-(CH_2)_q-R^4$;

when q is 0 to 2 R^4 is selected from hydrogen, C_{1-6}alkyl, $-C_{3-7}$cycloalkyl, $CONHR^5$, phenyl optionally substituted by R^7 and/or R^8, heteroaryl optionally substituted by R^7 and/or R^8 and heterocyclyl optionally substituted by R^7 and/or R^8;

and when q is 2 R^4 is additionally selected from C_{1-6}alkoxy, $NHCOR^5$, $NHCONHR^5$, NR^5R^6, and OH;

R^5 is selected from hydrogen, C_{1-6}alkyl and phenyl wherein the phenyl group may be optionally substituted by up to two substituents selected from C_{1-6}alkyl and halogen;

R^6 is selected from hydrogen and C_{1-6}alkyl;

or R^5 and R^6, together with the nitrogen atom to which they are bound, form a five- to six-membered heterocyclic or heteroaryl ring optionally containing up to one additional heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring may be substituted by up to two C_{1-6}alkyl groups;

R^7 is selected from C_{1-6}alkyl, C_{1-6}alkoxy, -$CONR^9R^9$, -$NHCOR^9$, -SO_2NHR^9, -$NHSO_2R^9$, halogen, trifluoromethyl, -Z-$(CH_2)_s$-phenyl optionally substituted by one or more halogen atom, –Z-$(CH_2)_s$-heterocyclyl or –Z-$(CH_2)_s$-heteroaryl wherein the heterocyclyl or heteroaryl group may be optionally substituted by one or more substituents selected from C_{1-6}alkyl;

R^8 is selected from C_{1-6}alkyl and halogen;

or when R^7 and R^8 are ortho substituents, then together with the carbon atoms to which they are bound, R^7 and R^8 may form a five- or six-membered saturated or unsaturated ring to give a fused bicyclic ring system, wherein the ring that is formed by R^7 and R^8 may optionally contain one or two heteroatoms selected from oxygen, nitrogen and sulfur;

R^9 is selected from hydrogen and C_{1-6}alkyl;

U is selected from methyl and halogen;

W is selected from methyl and chlorine;

V and Y are each selected independently from hydrogen, methyl and halogen;

Z is selected from -O- and a bond;

m and n are independently selected from 0, 1 and 2, wherein each carbon atom of the resulting carbon chain may be optionally substituted with up to two groups selected independently from C_{1-6}alkyl, and the sum of m+ n is from 0 to 4;

p is selected from 0 and 1;

q and s are selected from 0, 1 and 2;

r is selected from 0, 1 and 2;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1 wherein R^1 is optionally substituted by up to three substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, oxy, halogen, hydroxyC_{1-6}alkyl, -$N(C_{1-6}alkyl)_2$, -CH_2-$N(C_{1-6}alkyl)_2$, -CO_2C_{1-6}alkyl, phenyl optionally substituted by halogen and benzyl optionally substituted by halogen and/or cyano.

3. A compound according to claim 1 or 2 wherein X is optionally substituted phenyl, and R^1 is selected from optionally substituted pyrrolidinyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, tetrazolyl, oxazolyl, oxadiazolyl, piperidinyl, piperazinyl, morpholino, pyridyl, pyrimidinyl, thienyl, imidazolidinyl, benzimidazolyl and quinolyl; wherein the optional substituents for R^1 are selected independently from C_{1-6}alkyl, C_{1-6}alkoxy, oxy, halogen, hydroxyC_{1-6}alkyl, -$N(C_{1-6}alkyl)_2$ and -CH_2-$N(C_{1-6}alkyl)_2$.

4. A compound according to claim 1 or 2 wherein X is a bond, and R^1 is selected from an optionally substituted pyrrolidinyl, isoxazolyl, furyl, thienyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, thiazolyl, oxadiazolyl, piperidinyl, piperazinyl, morpholino, pyridyl, tetrahydrofuranyl, tetrahydrothiophenyl and quinolyl; wherein the optional

substituents for R^1 are selected independently from C_{1-6}alkyl, C_{1-6}alkoxy, oxy, halogen, hydroxyC_{1-6}alkyl, -$N(C_{1-6}alkyl)_2$, -CH_2-$N(C_{1-6}alkyl)_2$, -CO_2C_{1-6}alkyl, phenyl optionally substituted by halogen and benzyl optionally substituted by halogen and/or cyano.

5. A compound according to any one of the preceding claims wherein R^2 is selected from hydrogen, C_{1-4}alkyl and –CH_2-cyclopropyl.

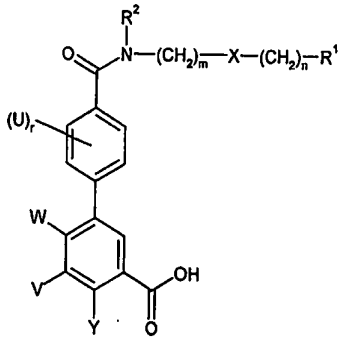
6. A compound according to any one of the preceding claims wherein m and n are independently selected from 0, 1 and 2, and the sum of m+n is from 0-3.

7. A compound according to any one of the preceding claims wherein R^4 is selected from C_{1-4}alkyl, cyclopropyl, -CH_2-cyclopropyl, pyridinyl and phenyl.

8. A compound according to claim 1 as defined in any one of Examples 1 to 26, or a pharmaceutically acceptable salt or solvate thereof.

9. A process for preparing a compound according to any one of claims 1 to 8 which comprises:

(a) reacting a compound of formula (XIII)



(XIII)

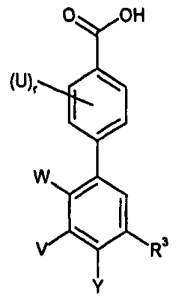
wherein R^1, R^2, X, U, W, V, Y, m, n and r are as defined in claim 1, with a compound of formula (XIV)

R^4-$(CH_2)_q$-NH_2

(XIV)

wherein R^4 and q are as defined in claim 1,
under amide forming conditions, optionally converting the acid compound (XIII) to an activated form of the acid before reaction with the amine compound (XIV);

(b) reacting a compound of formula (XV)



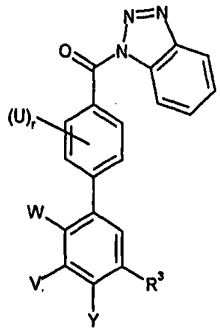
(XV)

wherein R^3, U, W, V, Y and r are as defined in claim 1,
with a compound of formula (XVI)

$$R^1(CH_2)_nX(CH_2)_mNR^2H \quad \text{(XVI)}$$

wherein R^1, R^2, X, m and n are as defined in claim 1,
under amide forming conditions;

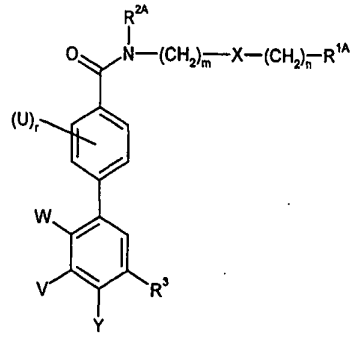
(c) reacting a compound of formula (XVII)



(XVII)

wherein R^3, U, W, V, Y and r are as defined in claim 1,
with a compound of formula (XVI) as defined above; or

(d) functional group conversion of a compound of formula (XVIII)



(XVIII)

wherein R^3, X, U, W, V, Y, m, n and r are as defined in claim 1 and R^{1A} and R^{2A} are R^1 and R^2 as defined in claim 1 or groups convertible to R^1 and R^2,
to give a compound of formula (I).

10. A pharmaceutical composition comprising a compound according to any one of claims 1 to 8 or a pharmaceutically acceptable salt or solvate thereof, in admixture with one or more pharmaceutically acceptable carriers, diluents or excipients.

11. A method for treating a condition or disease state mediated by p38 kinase activity or mediated by cytokines produced by the activity of p38 kinase comprising administering to a patient in need thereof a compound according to any one of claims 1 to 8 or a pharmaceutically acceptable salt or solvate thereof.

12. A compound according to any one of claims 1 to 8 or a pharmaceutically acceptable salt or solvate thereof for use in therapy.

13. Use of a compound according to any one of claims 1 to 8 or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for use in the

treatment of a condition or disease state mediated by p38 kinase activity or mediated by cytokines produced by the activity of p38 kinase.

INTERNATIONAL SEARCH REPORT

Internatio Application No
PCT/EP 02/11573

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/40 A61K31/341 A61K31/417 A61K31/4409 A61K31/4453
A61K31/4465 A61K31/426 A61K31/495 A61K31/5375 C07D211/26
C07D277/28 C07D295/12 C07D295/18 C07D307/14 C07D307/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 849 256 A (JAPAN TOBACCO INC) 24 June 1998 (1998-06-24) page 124 -page 125; claim 1 page 129 -page 130; claim 13 page 130; claim 16	1-8, 10-14
A	WO 00 41698 A (RIEDL BERND ;LOWINGER TIMOTHY B (JP); DUMAS JACQUES (US); RENICK J) 20 July 2000 (2000-07-20) the whole document	1-14

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 February 2003	26/02/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax (+31–70) 340–3016	Fink, D

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INTERNATIONAL SEARCH REPORT

Internatic application No
PCT/EP 02/11573

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D233/61

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

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Date of the actual completion of the international search	Date of mailing of the international search report
17 February 2003	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fink, D

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Internatic application No
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Form PCT/ISA/210 (patent family annex) (July 1992)